P TENT COOPERATION TREA

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 May 2001 (02.05.01)	
International application No. PCT/GB00/02664	**Applicant's or agent's file reference** APWO00659
International filing date (day/month/year) 11 July 2000 (11.07.00)	**Priority date** (day/month/year) 12 July 1999 (12.07.99)
Applicant SIEBOLD, Bernhard et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

09 February 2001 (09.02.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Pascal Piriou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

TENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

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Date of mailing (day/month/year)
22 March 2002 (22.03.02)

Applicant's or agent's file reference
APWO00659

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/02664

International filing date (day/month/year)
11 July 2000 (11.07.00)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

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State of Residence: DE
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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

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3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/03741 A1

(51) International Patent Classification[7]: A61K 47/26, 38/27

(21) International Application Number: PCT/GB00/02664

(22) International Filing Date: 11 July 2000 (11.07.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9916252.1 12 July 1999 (12.07.1999) GB
9918902.9 12 August 1999 (12.08.1999) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

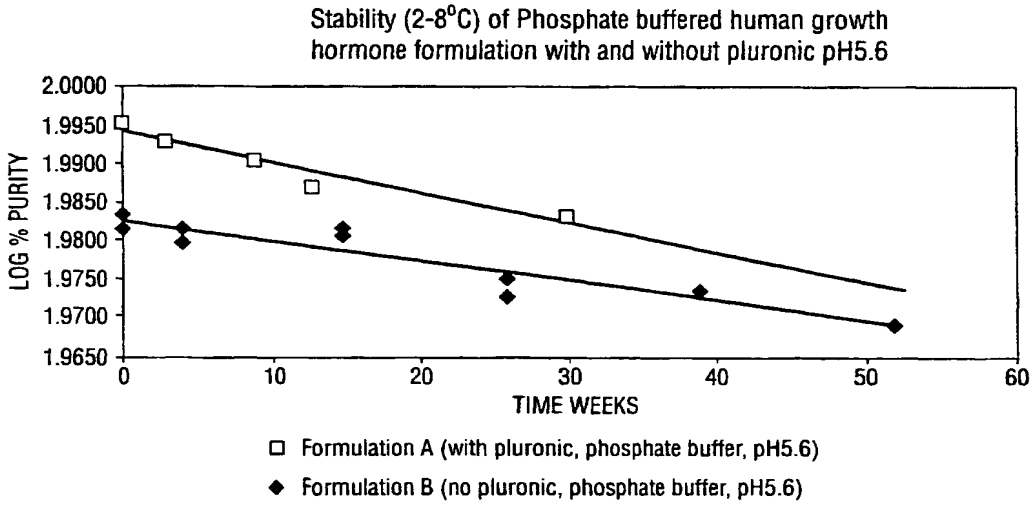
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *With amended claims.*

Date of publication of the amended claims: 19 April 2001

[Continued on next page]

(54) Title: GROWTH HORMONE FORMULATIONS



(57) Abstract: Liquid growth hormone formulations are storage stable for more than six months at temperatures in the range 2-8 °C by simply formulating growth hormones in phosphate buffer with no other additives at around physiological pH. By ensuring a pH of about 6.2 or greater, growth hormone crystallisation during storage at refrigeration temperatures or above is inhibited or reduced. Low concentrations of non-ionic surfactant can help to reduce aggregation of growth hormone arising as a result of physical forces encountered during automated transfer of bulk formulation into dosage containers. Mannitol is included in order to provide an isotonic formulation. Preservatives are included to reduce bacterial contamination and thereby permit multiple dosage units which can be stored at 2-8 °C.

WO 01/03741 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

AMENDED CLAIMS

[received by the International Bureau on 23 January 2001 (23.01.01);
original claims 1-34 replaced by amended claims 1-35 (4 pages)]

1. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution.

2. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution and a preservative.

3. A formulation as claimed in claim 1 or claim 2, wherein the compound conferring isotonicity is selected from one or more of monosaccharides, disaccharides and sugar alcohols.

4. A formulation as claimed in any one of claims 1 to 3, wherein the isotonicity is conferred by mannitol and/or sucrose, optionally lactose.

5. A formulation as claimed in any one of claims 1 to 4 having a pH in the range 5.6 to 6.5, or a pH of 6.2 or more.

6. A formulation as claimed in any of one claims 1 to 4 having a pH in the range 6.15 to 7.4, preferably a pH in the range 6.2 to 6.5.

7. A formulation as claimed in any of claims 2 to 6, wherein the preservative is selected from one or more of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride and benzethonium chloride.

8. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in phosphate buffered solution.

9. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in phosphate buffered solution and a preservative.

10. A storage stable liquid growth hormone formulation comprising growth hormone in phosphate buffered solution and a non-ionic surfactant in a

concentration of about 0.2% (w/v) or less.

11. A formulation as claimed in claim 10, wherein the non-ionic surfactant is present in a concentration of less than about 0.1% (w/v), more preferably 0.01% (w/v), even more preferably 0.001% (w/v).

12. A formulation as claimed in claim 10 or claim 11, wherein the phosphate buffered solution is isotonic, optionally with a pH in the range 5.6 to 6.5 and preferably further comprising a preservative.

13. A formulation as claimed in claim 12, wherein the preservative is selected from one or more of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride and benzethonium chloride.

14. A formulation as claimed in claim 12, wherein the isotonicity of the phosphate buffered solution is provided by a neutral salt, eg NaCl; or a compound selected from a monosaccharide, eg lactose; a disaccharide, eg sucrose; or a sugar alcohol, eg mannitol.

15. A formulation as claimed in any preceding claim, wherein the growth hormone is human.

16. A formulation as claimed in any preceding claim in which the growth hormone exhibits less than 0.01% aggregation, preferably less than 0.1%, more preferably less than 1%, even more preferably less than 10% aggregation.

17. A liquid growth hormone formulation of the following composition:

hGH	3.33mg/ml	(10 IU/ml)
$NaH_2PO_4.2H_2O$	0.85mg/ml	(ie 10mM phosphate buffer)
$Na_2HPO_4.7H_2O$	0.31mg/ml	
Mannitol	35mg/ml	(3.5% w/v)
Pluronic F-68	2mg/ml	(0.2% w/v)
Benzyl alcohol	9mg/ml	(0.9% v/v)

Water for injection q.s.
pH 6.2

18. A formulation as claimed in any preceding claim having no detectable crystallisation on storage.

19. A formulation as claimed in claim 18, wherein storage is for at least one month, preferably six weeks, more preferably a period in the range of about 1 month to 4 months, most preferably 3 months.

20. A formulation as claimed in claim 18 or claim 19, wherein the storage temperature is about 2°C or greater, preferably about 4°C or greater, more preferably a temperature in the range from about 2°C to less than 40°C, even more preferably a temperature in the range from about 2°C to 25°C, most preferably 15°C.

21. A formulation as claimed in any of claims 18 to 20, wherein the crystallisation is of growth hormone.

22. A formulation as claimed in any of claims 18 to 21, wherein the crystallisation is detected by eye, preferably under the light microscope at 5x magnification, more preferably under the light microscope at 10x magnification.

23. A device for administering a liquid to a subject by injection and loaded for use with at least one dosage unit of the formulation of any of claims 1 to 22.

24. A device as claimed in claim 23 being a pen injector device.

25. A device as claimed in claim 23 or claim 24, wherein the subject is a human.

26. A kit comprising an injection device and a separate container of a formulation of any of claims 1 to 22.

27. A kit as claimed in claim 26, wherein the container is adapted to engage with the injection device such that in use the formulation in the container is in fluid connection with the outlet of the injection device.

28. A kit as claimed in claim 27, wherein the injection device is a pen injector and the container is a cartridge.

29. A cartridge containing a liquid formulation of any of claims 1 to 22 for use with a pen injector device.

30. The use of an aqueous formulation of growth hormone comprising phosphate buffer at a pH of about 6.2 or more as a stored pharmaceutical product substantially free of crystallisation.

31. A use as claimed in claim 30, wherein the pH of the phosphate buffer is in the pH range 6.15 to 7.4, and/or the storage is for at least one month, and/or the storage temperature is about 2°C or more.

32. A use as claimed in claim 30 or claim 31, wherein the formulation comprises a non-ionic surfactant, preferably at a concentration of about 0.2% (w/v).

33. A method of avoiding crystallisation on storage of a phosphate buffered aqueous growth hormone formulation comprising formulating the growth hormone so that the formulation has a pH of about 6.2 or more.

34. A method as claimed in claim 32, wherein the pH is in the range 6.15 to 7.4, preferably 6.2 to 6.5, and/or the storage is for at least one month, and/or the storage temperature is about 2°C or more.

35. A method as claimed in claim 33 or claim 34, wherein the formulation comprises a non-ionic surfactant, preferably at a concentration of about 0.2% (w/v).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
APWO00659		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/02664	11/07/2000	12/07/1999
International Patent Classification (IPC) or national classification and IPC A61K47/26		
Applicant GRANDIS BIOTECH GMBH et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09/02/2001	27.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hornich, E Telephone No. +49 89 2399 8721

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/02664

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-20	as published			

Claims, No.:

1-9,10 (part),17 (part), 18-35	as received on	26/01/2001	with letter of	23/01/2001
10 (part),11-16, 17 (part)	as received on	16/11/2001	with letter of	14/11/2001

Drawings, sheets:

1/3-3/3	as published

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 30-32.

because:

   ☒ the said international application, or the said claims Nos. 30-32 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;

citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 13, 17, 26-29
	No:	Claims	10-12, 14-16, 18-25, 30-35
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-35
Industrial applicability (IA)	Yes:	Claims	1-29, 33-35
	No:	Claims	

2. Citations and explanations
see separate sheet

SECTION I

1. Amended claims 1-35 had been filed (23/01/01) according to **Art. 19 PCT** after the issue of the International Search Report, but - *by mistake - had not been considered as basis for the written opinion*, which was given on basis of the originally filed claims. The application was also published with the claims filed on 23/01/01.

   The *International Preliminary Examination Report* is being drafted on basis of amended claims 1-10(partly) and 17(partly)-35 filed with letter of 23/01/01 according to **Art. 19 PCT** and claims 10(partly)-17(partly) according to **Art. 34(2) PCT** after the issue of the written opinion.

2. The amendments appear to be ***allowable*** in the sense of **Art. 19(2)** and **34(2)(b) PCT**.

SECTION III

3. Claims 30-32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

SECTION V

4. Reference is made to the following documents:

   D1: WO 94 03198 A
   D2: US-A-5 567 677
   D3: US-A-5 610 134
   D4: US-A-5 126 324
   D5: US-A-5 096 885
   D6: WO 97 29767 A

5. *Novelty* (**Art. 33(2) PCT**)

5.1 **D1** discloses a *stable* aqueous formulation (and its use) containing *human growth hormone*, a *buffer* (e.g. *phosphate*), a *non-ionic surfactant* (0.1%-5% resp. 1%, 0.2% - see table III), and optionally, a *neutral salt* (--> 'adjusted to *near isotonicity*'), *mannitol* (or sugars/sugar alcohols, e.g. sorbitol, lactose) or a *preservative* (phenol, benzyl alcohol, meta-cresol, paraben, benzalconium / benzethonium chloride) (pH 4-8, preferably pH 6.0; administration with *jet injector guns*).
(see: abstract; p. 3, l. 30; p. 5, l. 27 - p. 6, l. 38; claims 1, 2, 10 and 14).

Thus, **D1** is **prejudicial to the novelty** of claims 30, 32, 33 and 35.

5.2 **D2** involves injectable, *isotonic* (aqueous) formulations of (*human*) *growth hormone* comprising *(h)GH*, a *buffer* (*citrate, but comparative solutions: phosphate*, see the tables, *pH 6.1-6.3, 7.4*), *sugar alcohols* (*mannitol*) and *preservatives* (*benzyl alcohol*). Surfactants are not included.
(see: abstract; col. 3, l. 7-29 and *44-46*; tables 1-3; claims 1, 2, 3, 12, 13, 16, 24, 27).

D2 thus **anticipates** the subject-matter of claims 30, 31, 33 and 34.

5.3 **D3** and **D4** disclose formulations *similar* to those already described in **D1** and **D2**. The disclosure within **D4** (phosphate buffer, pH 7.4-7.8; 0.1% non-ionic surfactant) **takes away the novelty** of claims 30-35.
(**D4**: col. 5, l. 10-15; col. 7, l. 13; col. 9, l. 38 - col. 10, l. 22, esp. l. 20).

5.4 As well, similar compositions are described within **D5** and **D6**; *isotonicity* is inherently disclosed as being a matter of routine for injectable formulations. (**D5**: ***about 0.001%***, above 0.01%, 0.1-5% ***polysorbate*** **(col. 6, l. 12, 15, 41)**; **D6**: 0.01%-5.0%, ... surfactant, addition of *isotonic modifiers*)
(**D5**: abstract; col. 2, l. 65 - col. 3, l. 20; col. 4, l. 50-68; col. 5, l. 44f.; col. 6, l. 5f., l. 12-15, l. 25, l. 37, l. 40f.; claims 1, 3, 8-17, 21; **D6**: p. 4, l. 16-24; p. 5, l. 15, 18, 23, 29; p. 6, l. 1-3 and l. 25; p. 8, l. 8-12, 18 and 25f.; p. 9, l. 21-29; p. 10, l. 15, p. 11, l. 4-6; p. 16, l. 1-3; p. 18, l. 5f.; p. 19, l. 12f. and 26f.).

The characteristics of the formulations and means for administration are such that

D5 anticipates the subject-matter of claims 10, 11 ('*less than* ***about*** *0.001% (w/v)*' (claim 11) and '***about*** *0.001% (w/v)*' in **D5**, col. 6, l. 12 appears to be the same), 12, 14 (*mannitol*), 15, 16, 18-25 and 30-35, and **D6 takes away the novelty** of claims 30, 32, 33 and 35.

5.5 To summarize, **novelty cannot be acknowledged** for claims 10-12, 14-16, 18-25 and 30-35.
The subject-matter of claims 1-9, 13, 17 and 26-29 appears to be **novel**.

6. *Inventive Step* (**Art. 33(3) PCT**)

6.1 The *problem* to be solved in the present application is to provide a *sufficiently stable, instantly usable liquid formulation of growth hormone avoiding or minimizing the use of pharmaceutically unacceptable or undesirable components* (like additional stabilising agents).

The *solution* of the present application resides in the provision of a *liquid growth hormone formulation* consisting essentially of *growth hormone in isotonic phosphate buffered solution* (claim 1).

6.2 The above-mentioned problem has already been the matter of concern of the above-cited documents **D1**, **D2**, **D5** and **D6**, disclosing compositions which additionally comprise *further ingredients*, such as stabilising agents, which represents the ***difference*** between the present application and the prior art (see e.g. **D1**, claim 1: '*A .... aqueous formulation of human growth hormone comprising human growth hormone, a buffer, a non-ionic surfactant, optionally ....* ').

6.3 The experiments of the present application show that compositions comprising a *phosphate buffer* are more stable than those comprising a *citrate buffer*; however, it appears that *compositions which do not comprise a non-ionic surfactant* are *not as stable as compositions comprising a non-ionic surfactant*. No data concerning stability is shown for Formula VI being the subject-matter of claim 17.

6.4 In addition, it is stated that a *pH value of at least 6.2* (and above) is necessary in order to avoid crystallisation (p. 20, l. 16f.). This gives rise to the supposition that a *pH value of at least 6.2* represents an *essential feature*; however, the compositions described in the experimental part of the application have *pH values of 6.0 and below*.

6.5 For the above-mentioned reasons, a positive conclusion with regard to **inventive step** can presently **not** be reached for claims 1-9, 13, 17 and 26-29.

7. *Industrial Applicability* (**Art. 33(4) PCT**)

7.1 The requirements of industrial applicability are fulfilled for claims 1-29 and 33-35.

7.2 For the assessment of the present claims 30-32 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims

1. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution.

2. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in isotonic phosphate buffered solution and a preservative.

3. A formulation as claimed in claim 1 or claim 2, wherein the compound conferring isotonicity is selected from one or more of monosaccharides, disaccharides and sugar alcohols.

4. A formulation as claimed in any one of claims 1 to 3, wherein the isotonicity is conferred by mannitol and/or sucrose, optionally lactose.

5. A formulation as claimed in any one of claims 1 to 4 having a pH in the range 5.6 to 6.5, or a pH of 6.2 or more.

6. A formulation as claimed in any of one claims 1 to 4 having a pH in the range 6.15 to 7.4, preferably a pH in the range 6.2 to 6.5.

7. A formulation as claimed in any of claims 2 to 6, wherein the preservative is selected from one or more of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride and benzethonium chloride.

8. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in phosphate buffered solution.

9. A storage stable liquid growth hormone formulation consisting essentially of growth hormone in phosphate buffered solution and a preservative.

10. A storage stable liquid growth hormone formulation comprising growth hormone in phosphate buffered solution and a non-ionic surfactant in a

concentration of about less than 0.01% (w/v).

11. A formulation as claimed in claim 10, wherein the non-ionic surfactant is present in a concentration of less than about 0.001% (w/v).

12. A formulation as claimed in claim 10 or claim 11, wherein the phosphate buffered solution is isotonic, optionally with a pH in the range 5.6 to 6.5 and preferably further comprising a preservative.

13. A formulation as claimed in claim 12, wherein the preservative is selected from one or more of phenol, benzyl alcohol, meta-cresol, methyl paraben, propyl paraben, benzalkonium chloride and benzethonium chloride.

14. A formulation as claimed in claim 12, wherein the isotonicity of the phosphate buffered solution is provided by a neutral salt, eg NaCl; or a compound selected from a monosaccharide, eg lactose; a disaccharide, eg sucrose; or a sugar alcohol, eg mannitol.

15. A formulation as claimed in any preceding claim, wherein the growth hormone is human.

16. A formulation as claimed in any preceding claim in which the growth hormone exhibits less than 0.01% aggregation, preferably less than 0.1%, more preferably less than 1%, even more preferably less than 10% aggregation.

17. A liquid growth hormone formulation of the following composition:

hGH	3.33mg/ml	(10 IU/ml)
$NaH_2PO_4.2H_2O$	0.85mg/ml	(ie 10mM phosphate buffer)
$Na_2HPO_4.7H_2O$	0.31mg/ml	
Mannitol	35mg/ml	(3.5% w/v)
Pluronic F-68	2mg/ml	(0.2% w/v)
Benzyl alcohol	9mg/ml	(0.9% v/v)
Water for injection	q.s.	

~~Water for injection~~ q.s.

pH 6.2

18. A formulation as claimed in any preceding claim having no detectable crystallisation on storage.

19. A formulation as claimed in claim 18, wherein storage is for at least one month, preferably six weeks, more preferably a period in the range of about 1 month to 4 months, most preferably 3 months.

20. A formulation as claimed in claim 18 or claim 19, wherein the storage temperature is about 2°C or greater, preferably about 4°C or greater, more preferably a temperature in the range from about 2°C to less than 40°C, even more preferably a temperature in the range from about 2°C to 25°C, most preferably 15°C.

21. A formulation as claimed in any of claims 18 to 20, wherein the crystallisation is of growth hormone.

22. A formulation as claimed in any of claims 18 to 21, wherein the crystallisation is detected by eye, preferably under the light microscope at 5x magnification, more preferably under the light microscope at 10x magnification.

23. A device for administering a liquid to a subject by injection and loaded for use with at least one dosage unit of the formulation of any of claims 1 to 22.

24. A device as claimed in claim 23 being a pen injector device.

25. A device as claimed in claim 23 or claim 24, wherein the subject is a human.

26. A kit comprising an injection device and a separate container of a formulation of any of claims 1 to 22.

27. A kit as claimed in claim 26, wherein the container is adapted to engage with the injection device such that in use the formulation in the container is in fluid connection with the outlet of the injection device.

28. A kit as claimed in claim 27, wherein the injection device is a pen injector and the container is a cartridge.

29. A cartridge containing a liquid formulation of any of claims 1 to 22 for use with a pen injector device.

30. The use of an aqueous formulation of growth hormone comprising phosphate buffer at a pH of about 6.2 or more as a stored pharmaceutical product substantially free of crystallisation.

31. A use as claimed in claim 30, wherein the pH of the phosphate buffer is in the pH range 6.15 to 7.4, and/or the storage is for at least one month, and/or the storage temperature is about 2°C or more.

32. A use as claimed in claim 30 or claim 31, wherein the formulation comprises a non-ionic surfactant, preferably at a concentration of about 0.2% (w/v).

33. A method of avoiding crystallisation on storage of a phosphate buffered aqueous growth hormone formulation comprising formulating the growth hormone so that the formulation has a pH of about 6.2 or more.

34. A method as claimed in claim 32, wherein the pH is in the range 6.15 to 7.4, preferably 6.2 to 6.5, and/or the storage is for at least one month, and/or the storage temperature is about 2°C or more.

35. A method as claimed in claim 33 or claim 34, wherein the formulation comprises a non-ionic surfactant, preferably at a concentration of about 0.2% (w/v).

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
APW000659		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 02664	11/07/2000	12/07/1999
Applicant		
GRANDIS BIOTECH GMBH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [X] as suggested by the applicant.

   [ ] None of the figures.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted]B 00/02664

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/26 A61K38/27

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 03198 A (GENENTECH INC ;CONNOR BARBARA H O (US); OESWEIN JAMES Q (US)) 17 February 1994 (1994-02-17) page 5, line 18 -page 11, line 27 claims 1-21 ---	1-34
X	US 5 567 677 A (HOEKBY ELVY ET AL) 22 October 1996 (1996-10-22) column 3, line 6 - line 34 column 4; table 1 column 7; table 3 claim 1 --- -/--	1-8, 11-15, 17-21, 23-34

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 November 2000	24/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Muller, S

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]B 00/02664

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 096 885 A (OESWEIN JAMES Q ET AL) 17 March 1992 (1992-03-17) column 2, line 65 -column 3, line 20 column 4, line 21 -column 5, line 53 claims 1-3,10,13,14,22	1-6, 9-11, 14-21, 23-34
X	US 5 610 134 A (CLARK ROSS G ET AL) 11 March 1997 (1997-03-11) column 12, line 42 -column 13, line 13	1-3,5, 9-11,14, 15, 19-21, 23-34
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A	WO 97 29767 A (CSL LTD ;UNIV MONASH (AU); MCNAMARA MICHAEL KEVIN (AU); CHARMAN WI) 21 August 1997 (1997-08-21) page 4, line 16 -page 9, line 17 page 15; table 2 page 17; table 4 claims 1-11	22

1

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